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Phase II study of berzosertib + topotecan in patients with relapsed platinum-resistant SCLC (DDRiver SCLC 250): Japanese safety run-in

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CONCLUSIONS

Berzosertib 210 mg/m² (days 2, 5) + topotecan 1.25 mg/m² (days 1–5) administered intravenously (IV) in 21-day cycles was well tolerated by Japanese patients with relapsed platinum-resistant small-cell lung cancer (SCLC)

At the recommended Phase II dose (RP2D), pharmacokinetic parameters were approximately similar in Japanese and non-Japanese patients

The RP2D for Japanese patients was the same as for the global study population

BACKGROUND

- SCLCs are characterised by a high degree of genomic instability and DNA replication stress[1]
- Ataxia-telangiectasia–mutated and rad3-related (ATR) protein kinase is a key regulator of the DNA damage response (DDR), which helps stabilise the genome under conditions of replication stress.[1] Therefore, ATR inhibition in combination with chemotherapy may be a rational treatment strategy for SCLC
- Berzosertib (formerly M6620) is a potent and selective IV-administered small-molecule ATR inhibitor[2] that is currently being investigated in combination with DNA damage-inducing chemotherapy in several solid tumour types
- Berzosertib + topotecan showed antitumour activity and was well tolerated in patients with relapsed SCLC in a single-arm phase I/II study (NCT02487095)[1,3]
- The DDRiver SCLC 250 trial (NCT04768296) was designed to evaluate the efficacy and safety of berzosertib + topotecan in patients with relapsed, platinum-resistant SCLC[4]
- We present data from the Japanese safety run-in part of the study; these are the first data for berzosertib in combination with any chemotherapy in Japanese patients

STUDY DESIGN

Safety run-in (Japan only)

- Dose escalation followed a Bayesian Optimal Interval Design
- Japanese patients (n=3–9) with advanced solid tumours received dose level (DL) 1: berzosertib 105 mg/m² (days 2, 5) + topotecan 1.25 mg/m² (days 1–5) IV in 21-day cycles until disease progression or unacceptable toxicity (**Figure 1**)
- If DL1 was tolerated, Japanese patients with relapsed, platinum-resistant SCLC (n=3–9) were to be enrolled to receive DL2 (berzosertib 210 mg/m²), which was the same dose as the primary cohort

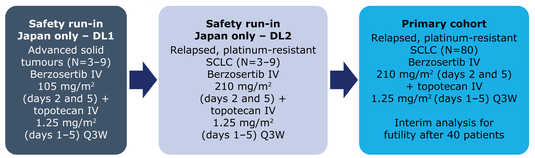
Primary cohort (main part of the study)

- Japanese and non-Japanese patients with relapsed, platinum-resistant SCLC (n≈80) received berzosertib 210 mg/m² (days 2, 5) + topotecan 1.25 mg/m² (days 1–5) IV in 21-day cycles until disease progression or unacceptable toxicity

Assessment of dose-limiting toxicities

- Participants were monitored for dose-limiting toxicities (DLTs) during cycle 1 (21 days)
- Cohorts of three patients were to be enrolled. At least three DLT-evaluable patients per dose level were required to confirm tolerability

Figure 1. Study design



Primary/secondary prophylactic GCSF was highly recommended and could be administered according to local practice
DL, dose level; **GCSF**, granulocyte-colony stimulating factor; **IV**, intravenous; **Q3W**, every 3 weeks; **SCLC**, small cell lung cancer

- Key eligibility criteria are shown in **Table 1**
- Objectives and endpoints for the Japanese safety run-in part are shown in **Table 2**
- The Japanese safety run-in part was analysed separately from the primary cohort
- Safety analyses were conducted separately for DL1 and DL2

STUDY DESIGN CONTINUED

Table 1. Key eligibility criteria

	Key inclusion criteria	Key exclusion criteria
Japanese safety run-in, DL1	• Histologically confirmed advanced solid tumours • ECOG PS ≤1 and Karnofsky scale ≥70%	• Prior treatment with ATR inhibitor • Prior treatment with TOP1 inhibitor • Unstable brain metastases • Clinically relevant (i.e. active), uncontrolled intercurrent illness
Main study + Japanese safety run-in, DL2	• Histologically confirmed SCLC, with disease progression on/after first-line platinum-based treatment or chemoradiation, with or without immunotherapy, with a PFI* <90 days • Measurable disease per RECIST version 1.1 • ECOG PS ≤2 and Karnofsky scale ≥60%	

*PFI is defined as the time from the last day of a platinum-based treatment regimen to documented disease progression
ATR, ataxia telangiectasia and Rad3-related; **DL**, dose level; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **PFI**, platinum-free treatment interval; **RECIST**, Response Evaluation Criteria in Solid Tumours; **SCLC**, small-cell lung cancer; **TOP1**, topoisomerase 1

Table 2. Objectives and endpoints: Japanese safety run-in

Objectives	Endpoints
To confirm whether the RP2D of berzosertib + topotecan applies to Japanese patients (primary objective)	Occurrence of DLTs, AEs,* treatment-related AEs,* and changes in vital signs, clinical laboratory parameters and ECGs
To characterise the pharmacokinetic profile of berzosertib in Japanese patients	Pharmacokinetic parameters in plasma by non-compartmental analysis
To evaluate the efficacy of berzosertib + topotecan†	OR, DoR, PFS, by RECIST version 1.1, OS and QoL

*AEs were classified according to MedDRA version 24.1
†Efficacy outcomes were assessed by the investigators
AE, adverse event; **DLT**, dose-limiting toxicity; **DoR**, duration of response; **ECG**, electrocardiogram; **MedDRA**, the Medical Dictionary for Regulatory Activities; **OR**, overall response; **OS**, overall survival; **PFS**, progression-free survival; **QoL**, quality of life; **RECIST**, Response Evaluation Criteria in Solid Tumours; **RP2D**, recommended Phase II dose

RESULTS

Patient characteristics and disposition

- Baseline characteristics are shown in **Table 3**
- All six patients received primary prophylactic granulocyte-colony stimulating factor during the DLT period
- As of April 2022, four of the six patients remained on treatment, with disease having progressed in one patient at each dose level

Table 3. Baseline characteristics

	DL1 (n=3)	DL2 (n=3)
Male, n (%)	2 (66.7)	3 (100)
Mean age, years (SD)	51.3 (4)	58.7 (5)
Tumour type	Platinum-sensitive SCLC (n=1) Malignant pleural mesothelioma (n=1) Carcinosarcoma (n=1)	Platinum-resistant SCLC (n=3)
Brain metastases present at baseline, n (%)	0	1 (33.3)
Liver metastases present at baseline, n (%)	1 (33.3)	1 (33.3)
Prior use of immunotherapies, n (%)	2 (66.7)	3 (100.0)

DL, dose level; **SCLC**, small-cell lung cancer; **SD**, standard deviation

Safety

- Safety results are shown in **Table 4**. No DLTs were reported
- In addition to the events shown, one patient experienced a grade 1 creatinine increase that required topotecan dose adjustment

Table 4. Safety events

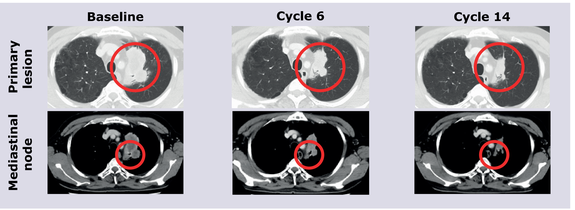
	DL1 (n=3)	DL2 (n=3)
DLT, n	0	0
TEAE grade ≥3, n	0	1*
Serious TEAE, n	0	1†
Any grade TEAE occurring in ≥2 patients, n		
Anaemia	3	2
Thrombocytopenia	3	3
Lipase increased	1	1
Leukopenia	0	2

*Four grade 3 events, all in the same patient: lymphocyte count decreased, lipase increased (asymptomatic), leukopenia and anaemia. None were classified as a serious AE
†One serious TEAE was reported after the DLT period (study day 37): lumbar spine compression fracture (grade 2, unrelated to study drugs)
AE, adverse event; **DL**, dose level; **DLT**, dose-limiting toxicity; **TEAE**, treatment-emergent adverse event

Efficacy

- At the data cut off in April 2022, one patient at DL1 with platinum-sensitive SCLC had a partial response (**Figure 2**)

Figure 2. CT scans of patient with partial response



CT, computed tomography

Pharmacokinetics

- Berzosertib exposure increased approximately proportionally between the 105 and 210 mg/m² dose levels
- At berzosertib 210 mg/m² + topotecan 1.25 mg/m², berzosertib area under the curve, maximum concentration, clearance and steady state volume of distribution were approximately similar in Japanese and non-Japanese patients (investigated in study NCT02487095[3]) (**Table 5**)

Table 5. Key plasma berzosertib pharmacokinetic parameters following IV infusion on Cycle 1 Day 2

	Japanese patients DDRiver SCLC 250		Non-Japanese patients Thomas et al.[3]
Berzosertib dose	**105 mg/m² (n=3)**	**210 mg/m² (n=3)**	**210 mg/m² (n=12)**
C_{max} (ng/mL)	259 (23)	446 (18)	574 (50)
$AUC_{0-\infty}$ (ng*hr/mL)	2480 (2)	4360 (10)	5103 (34)
$t_{1/2}$ (hr)	18.5 (7)	17.3 (12)	13 (18)
CL (L/hr)	77 (12)	84.3 (13)	80 (32)
V_{ss} (L)	1620 (15)	1770 (5)	1390 (34)

All values represented as geometric mean (CV% GeoMean); GeoMean of pharmacokinetic parameters for non-Japanese patients were calculated using the data provided in the supplemental material of Thomas et al. 2021[3]
AUC_{∞}, area under the curve extrapolated to time infinity; **CL**, clearance; **C_{max}**, maximum plasma concentration; **CV% GeoMean**, geometric coefficient of variation; **$t_{1/2}$**, half life, **V_{ss}**, steady state volume of distribution

Study closure

- Following a pre-planned interim analysis of the primary cohort, the DDRiver SCLC 250 study was closed for enrolment due to low probability of meeting the predefined efficacy objective

References: **1.** Thomas A, et al. J Clin Oncol 2018;36:1594–1602; **2.** Reaper PM, et al. Nat Chem Biol 2011;11:428–430; **3.** Thomas A, et al. Cancer Cell 2021;39:566–579; **4.** Thomas A, et al. Ann Oncol 2021;32(Suppl. 5):S1164–S1174

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